REFLECTIONS ON BETA-ADRENERGIC BLOCKADE IN ANAESTHETICS

BY

M. JOHNSTONE

HISTORICAL BACKGROUND

Sympathetic stimulation constricts the blood vessels of the skin and viscera and contracts the intestinal sphincters and the pilomotor muscles. Similar responses are elicited by adrenaline and are blocked by ergot (Dale, 1906). Adrenaline relaxes the non-pregnant feline uterus and the gall bladder. Cannon and Rosenblueth (1933) suggested that the differences in the effects of sympathetic stimulation on various viscera may have been due to the release of two different agonists, one for excitation (Sympathin E) and one for inhibition (Sympathin I). Von Euler (1946) indicated the need for another explanation when he showed that noradrenaline was released at sympathetic nerve endings.

Ahlquist (1948), who postulated the presence of two types of adrenergic receptors, showed that when sympathetic amines were tested on various smooth muscle preparations adrenaline and noradrenaline were most potent in one series, and isoprenaline in another. He suggested that one series had alpha (excitatory) receptors and the other had beta (inhibitory) receptors (table I). Cardiac tissue was exceptional, being sensitive to isoprenaline which increased the rate, the force of contraction and the speed of conduction of its electrical impulses. Drugs like dibenamine blocked the alphareceptors and had no effect on the beta receptors.

<table>
<thead>
<tr>
<th>Order of activity</th>
<th>Vasoconstriction (alpha receptor)</th>
<th>Tachycardia (beta receptor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adrenaline</td>
<td>Isoprenaline</td>
</tr>
<tr>
<td>2</td>
<td>Noradrenaline</td>
<td>Methyladrenaline</td>
</tr>
<tr>
<td>3</td>
<td>Methylnoradrenaline</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>4</td>
<td>Methyladrenaline</td>
<td>Methylnoradrenaline</td>
</tr>
<tr>
<td>5</td>
<td>Isoprenaline</td>
<td>Noradrenaline</td>
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</table>

Selective cardiac adrenergic blockade by dichloroisoproterenol (DCI). Vertical bars represent mean change in right ventricular contractile force in anaesthetized, vagotomized open chest dogs in response to i.v. injections of various cardiac stimulant drugs or to nerve stimulation. Open bars, control responses; hatched bars, responses after 15 mg/kg of DCI. A=adrenaline; N=noradrenaline; I=isoprenaline; S=right cardiac sympathetic nerve stimulation; Ca=calcium chloride; D=digoxin; T=theophylline. (Taken from Moran, N. C. (1966) by kind permission of the author and the University of Pennsylvania Press.)

Powell and Slater (1958) described the first drug, dichloroisoprenaline, which blocks the beta-adrenergic receptors. A beta receptor blocker may be defined as a substance which specifically, competitively and reversibly antagonizes the action of a catecholamine on the beta-adrenergic site (Barrett and Fitzgerald, 1968). A beta blocker prevents the positive cardiac inotropism of isoprenaline and has no effect on the positive inotropism of calcium or digitalis (fig. 1). The antagonism of a beta blocker to isoprenaline is overcome by an increased dose of the catecholamine. The dose response curve to isoprenaline after beta blockade...
Effect of I-Propranolol on Isoprenaline Tachycardia

Fig. 2

Increments in heart rate to ascending doses of isoprenaline in anaesthetized dogs before and after various doses of I-propranolol. (Reproduced from Barrett and Cullum (1968) by kind permission of British Journal of Pharmacology and Macmillan Ltd., London.)

is similar to the one before, but is moved to the right because larger doses of the agonist are required to achieve a similar effect (fig. 2). In addition to their effects on the cardiac adrenergic receptors most beta blockers antagonize the effects of catecholamines on the smooth muscle of the bronchioles and the blood vessels of the somatic musculature. They also prevent the release of lactate from muscle glycogen and free fatty acids and glycerol from triglycerides and suppress the mobilization of glucose during insulin-induced hypoglycaemia (Pilkington et al., 1966; Abramson, Arky and Woeber, 1966).

THE PHARMACOLOGY OF BETA BLOCKING DRUGS

This may be divided into beta blocking and other actions. A beta blocking drug specifically and competitively antagonizes the beta effects of catecholamines. The potency of such a drug can be determined by its ability to inhibit a standard isoprenaline-induced tachycardia in the dog. Several such drugs have been synthesized and include dichloroisoprenaline, pronethalol (Alder-lin), propranolol (Inderal), alprenolol (Betaptin), practolol (Eraldin), oxprenolol (Trasicor), butoxamine, N-isopropyl-p-nitrophenylthanolamine (dl-INPEA), Sotalol (MJ.1999) and butidrine. The essential pharmacological features of these compounds have been reviewed by Fitzgerald (1970). Propranolol is the reference blocker with which others are compared and is of similar potency to alprenolol. Oxprenolol has twice the potency of propranolol; dichloroisoprenaline, pronethalol, butidrine and Sotalol approximately one-tenth. Practolol has half the potency of propranolol and INPEA one twenty-fifth.

In addition to beta blocking action, some agents possess intrinsic sympathomimetic activity. This implies that when the antagonist interacts with the receptor not only does it block the access of the agonist but it also stimulates the receptor. The degree of stimulation is very low compared with isoprenaline (Barrett, personal communication) and can only be demonstrated in catecholamine-depleted (reserpinized) animals.

Some adrenergic blocking drugs depress the spike potential in stimulated isolated frog nerve and are therefore analgesic substances. Their local anaesthetic potency is unrelated to their beta blocking activity (Sharma, 1967). Large doses of beta blocking drugs which are local anaesthetics may be expected to impair the conductivity of the Purkinje tissue (negative dromotropism) and, for the same reason, to potentiate the action of depolarizing muscle relaxants (Wislicki and Rosenblum, 1967). The pharmacological features of the beta blocking drugs which have been used in clinical anaesthesia are as follows.

Dichloroisoprenaline.

This was introduced by Powell and Slater in 1958. It is an analgesic substance with strong sympathomimetic activity. The latter effect seems to have outweighed its beta blocking activity and curtailed its clinical study. Its successful use in the anaesthetic management of patients with phaeochromocytoma was reported by Riddell et al. (1963).

Pronethalol.

This drug was introduced by Black and Stephenson in 1962. It too is a local anaesthetic substance with a weak intrinsic sympathomimetic action. It has been used successfully to reverse
cardiac arrhythmias in anaesthetized patients (Payne and Senfield, 1964; Johnstone, 1964). The drug was withdrawn from clinical use when it was observed that prolonged administration of large doses causes thymic tumours in mice.

**Propranolol.**

Propranolol was introduced by Black, Duncan and Shanks in 1965. It is a local anaesthetic substance without sympathomimetic activity. The analgesic potency is sufficient to produce reversible lumbar plexus and subarachnoid nerve blocks in animals when applied locally (Jaju, Sinha and Sharma, 1969). It causes a slight prolongation of the atrioventricular conduction time, but unlike quinidine and procainamide, has no effect on intraventricular conduction (Berkowitz et al., 1969). It has been used successfully in the treatment of cardiac arrhythmias in anaesthetized patients (Hellewell and Potts, 1965; Johnstone, 1966; Bird et al., 1969). The effective dose in adults ranges between 0.5 and 10.0 mg according to the intensity of the adrenergic stimulus to be controlled.

Propranolol is a racemate capable of resolution into d- and l-isomers. The l-isomer has strong beta-adrenergic blocking activity, having twice the potency of racemic propranolol (Barrett and Cullum, 1968). The d-isomer is strongly anaesthetic and devoid of beta blocking activity: 10-mg doses intravenously in adults anaesthetized with halothane had no influence on sinus tachycardias and ventricular dysrhythmias of adrenergic origins.

**Alprenolol.**

It was introduced by Ablad, Brogard and Ek in 1967 and is a local anaesthetic with a weak intrinsic sympathomimetic action. Single intravenous doses up to 10 mg have been used successfully in adults anaesthetized with halothane to reverse cardiac irregularities.

**Oxprenolol.**

Oxprenolol was introduced by Brunner, Hedwall and Meier in 1968. It has local anaesthetic properties and a weak intrinsic sympathomimetic action. It has been used successfully in the treatment of angina pectoris (Wilson et al., 1968).

Preliminary studies of its effects in adult patients lightly anaesthetized with halothane in oxygen indicate it to be an effective beta blocking agent with twice the potency of propranolol (Johnstone, to be published).

**Practolol.**

This drug was introduced by Dunlop and Shanks in 1968. It has no local anaesthetic activity and a weak intrinsic sympathomimetic activity. Its beta blocking action is cardioselective, being without effect on the beta receptors of respiratory or vascular smooth muscle. It has been used successfully in anaesthetized patients in single intravenous doses up to 20 mg (Johnstone, 1969).

**Beta-adrenergic blockade and the anaesthetist**

Beta-adrenergic blockade is of interest to the anaesthetist for two reasons:

1. some patients on treatment with beta blockers will acquire coincidental surgical disease and it may be anticipated that the beta-adrenergic blockade may alter the cardiovascular reaction to surgical stress and to anaesthesia; and
2. beta-adrenergic blockade will be beneficial in the control of the undesirable cardiac reactions to the adrenergic stress of surgery and anaesthesia.

Beta-adrenergic blockade is now used in the treatment of angina pectoris, cardiac dysrhythmia, the hyperkinetic heart syndrome, hypertrophic obstructive cardiomyopathy and Fallot's tetralogy. It is also used in Parkinsonism, thyrotoxicosis, hypertension, phaeochromocytoma and glaucoma (Fitzgerald, 1970). At the moment there is little information on the reactions to acute surgical stresses (hypovolaemia, trauma, hypoxia and toxaemia) in patients on long-term therapy with beta blockers, but it may be assumed that the tolerance to such stresses may be diminished (Warner, 1968). Some causes of myocardial depression, notably metabolic acidosis and bacterial toxaemias, are counteracted by the myocardial stimulant (inotropic) effect of endogenous catecholamines; sympathetic blockade in these circumstances may precipitate cardiac failure (Thrower, Darby and Aldinger, 1961). Similarly, sympathetic blockade may cause heart failure in those heart diseases which require the unimpaired...
action of endogenous catecholamines to support the failing myocardium (Braunwald, 1965).

The author has encountered six patients who needed elective surgery after prolonged treatment of heart disease with propranolol. The operations were hysterectomy, prostatectomies and herniorrhaphy. In each case the oral propranolol was discontinued on the evening of the day preceding the operation and resumed 24 hours afterwards. In none of the patients did the cardiovascular behaviour before, during or after the operation vary from that observed in untreated patients in whom light halothane-oxygen-relaxant anaesthesia was used. The pre-operative treatment of thyrotoxicosis and phaeochromocytoma (Robertson, 1965) with beta blockers protects the heart from the adrenergic reactions likely to be provoked by surgery in these circumstances.

The induction of beta-adrenergic blockade in anaesthetized patients adds to the safety of anaesthesia when the blockade is induced in the correct circumstances. One of the functions of anaesthesia is to protect patients from the adrenergic reactions provoked by surgical trauma. The more obvious manifestations of hyperadrenergism are alpha vasoconstriction and beta overactivity of the heart affecting its chronotropic, inotropic, dromotropic and dysrhythmic activities. The easily detectable signs of hyperadrenergism are sinus and atrioventricular nodal tachyarrhythmias and the various forms of ventricular dysrhythmias. The more serious consequences of cardiac overactivity include a relative increase in myocardial hypoxia in patients with coronary insufficiency, an increase in the output of normal hearts which raises the peripheral blood flow and increases the bleeding from cut tissues in vasodilated subjects, and the possibility of ventricular fibrillation when the adrenergic stimulus is intense. The causes of adrenergic overactivity of the heart include diseases such as thyrotoxicosis and phaeochromocytoma, pre-operative fear, surgical manipulations and incisions during light anaesthesia, respiratory acidosis, injections of adrenaline or other catecholamines, and possibly hypothermia and hyperpyrexia. The susceptibility of the heart to adrenergic influence is increased by vagolytic drugs such as atropine or gallamine. No anaesthetic agent can fully protect the heart from the consequences of sympathetic stimulation. Some, like halothane or cyclopropane, increase the sensitivity of the beta-adrenergic receptors.

Prior to the discovery of beta-adrenergic blockade the more severe cardiac reactions to sympathetic stimuli were managed mainly by using the remedy appropriate to each particular cause of the sympathetic stimulation, e.g. adequate pre-operative sedation, gentle induction of anaesthesia, blockade of sensory afferent nerves with local analgesic substances, efficient ventilation, the use of anaesthetic agents which do not sensitize the receptors to catecholamines, and various other non-specific remedies such as activation of vagal reflexes (Johnstone, 1953) or the use of substances such as quinidine with local anaesthetic properties, the effect of which is essentially a widespread impairment of conduction within the Purkinje system. (Propanidid, the intravenous anaesthetic agent, possesses similar properties (Johnstone and Barron, 1968).)

**INDICATIONS FOR BETA-ADRENERGIC BLOCKADE IN SURGICAL PATIENTS**

**Pre-operative preparation.**

Beta-adrenergic blockade may be used to control the cardiac dysfunctions of thyrotoxicosis particularly when they are unresponsive to conventional therapy or when sensitivity develops to antithyroid drugs (Hofer et al., 1968; Shanks et al., 1969). When combined with alpha blockers, beta blockers are effective in the management of tachycardia in patients with phaeochromocytoma (De Blasi, 1966; Robertson, 1965). It is also effective in the control of the cardiac disturbances associated with anxiety (Turner, Granville-Grossman and Smart, 1965; Imhof et al., 1969) and digitalis intoxication (Turner, 1966). It may also be combined with local anaesthetics for dental and endoscopic procedures to prevent the cardiac reactions to cocaine or adrenaline (Orr and Jones, 1968; Machtens and Opitz, 1967).

**During anaesthesia.**

The obvious indication for beta-adrenergic blockade during anaesthesia is in the control of the adrenergic reactions of the heart which cannot be prevented in any other way. It is indicated in the management of the cardiac dysrhythmias provoked by catecholamine injections (Hellewell and Potts, 1965), by intraperitoneal insufflations
of carbon dioxide (Johnstone, 1969) and possibly in the management of the cardiac disturbances caused by surgical manipulations in the region of the fourth cranial ventricle (Whitby, 1963). In the interests of haemostasis the sinus tachycardias provoked by an excess of atropine or by surgical stimulation during light anaesthesia are easily controlled by beta-adrenergic blockade; the effect of the blockade is to diminish the peripheral blood flow by lowering the excessively high cardiac output (Johnstone and Horsfall, 1966; Hellewell and Potts, 1966; Hewitt, Lord and Thornton, 1967). It has also been used to control the cardiac dysrhythmias of induced hypothermia (Cole and Jacobs, 1967; Finlay and Dykes, 1968), and some of the dysrhythmias provoked by cardiac surgery (McClish et al., 1968; Muller and Dietzel, 1967).

Cardiac disturbances of thyrotoxic origin appearing during anaesthesia have also responded favourably to beta blockade (Bird et al., 1969). The malignant hyperpyrexia provoked by anaesthesia in experimental animals is unaffected by propranolol (Harrison et al., 1969).

Postoperative treatment.

Postoperative thyrotoxic crises have been successfully treated with beta blockers (Hughes, 1966; McLean, 1967; Parsons and Jewitt, 1967). A severe hyperpyrexia in a thyrotoxic patient responded dramatically to beta-adrenergic blockade after the failure of conventional measures (Das and Krieger, 1969). Beta blockers may also have a place in the treatment of cardiac dysfunctions in patients recovering from cardiac surgery (Matloff et al., 1968; Gibson, Balcon and Sowton, 1968). Small doses of beta blockers are also effective in preventing the undesirable cardiac dysrhythmias caused by methylphenidate which is used to abolish the muscular spasticity and clonus which complicate the recovery from halothane anaesthesia (Brichard and Johnstone, to be published)—methylphenidate is a cerebral stimulant with a sympathomimetic action on the heart. Atsmon and Blum (1970) have reported that propranolol causes a dramatic improvement in the signs and symptoms of acute porphyria variegata.

DANGERS OF BETA-ADRENERGIC BLOCKING DRUGS

The dangers of beta-adrenergic blockers are essentially those of beta-adrenergic blockade. The negative inotropism of beta blockade may be of serious consequence when applied to a myocardium already struggling against other negative inotropic influences. Reference has been made to the dangers of beta blockade in patients with incipient heart failure, heart block, toxaemias and diabetes mellitus (Warner, 1968). Bronchial asthma, latent or overt, is an absolute contraindication to the use of non-cardioselective beta blockers (McNeill, 1964). Practolol, a cardioselective blocker is the agent of choice in patients prone to asthma (Macdonald and McNeill, 1968).

Vagal inhibition of the heart, with the possibility of vagal arrest, is the major hazard of beta-adrenergic blockade in anaesthetized patients. It is avoided by atropinization. The fact that atropine does not cause sinus tachycardia in the presence of beta blockade does not indicate a decrease in its effectiveness as a cardiac cholinergic blocker. Neostigmine may therefore be used safely to reverse the effects of tubocurarine and other non-depolarizing neuromuscular blocking agents.

The choice of anaesthetic agent for use with beta-adrenergic blockade is important. It is reasonably well established that light halothane-oxygen anaesthesia is safely compatible when the blockade is used in the appropriate circumstances, i.e. when clear evidence of undesirable adrenergic overactivity is present or anticipated. The compatibility of halothane anaesthesia and beta-adrenergic blockade is probably related to the fact that the maintenance of myocardial function during halothane anaesthesia is not dependent on the release of endogenous catecholamines. Methoxyflurane is in a questionable position as its use with beta blockers in the few reported cases has been associated with circulatory collapses for reasons not necessarily related to anaesthesia (Vetten and Kundig, 1965; Black, Glasgow and Smith, 1969). The adrenergic cardiac dysrhythmias provoked by chloroform or cyclopropane anaesthesia in man have been controlled by beta blockade (Payne and Senfield, 1964).

Sekiya and Vaughan Williams (1965) reported that beta-adrenergic blockade caused cardiac arrest in atropinized guineapigs anaesthetized with ether or chloroform. Rouse (1966) stated that beta-adrenergic blockade caused fatal cardiac arrest in dogs anaesthetized with ether. Later, in different circumstances, he (1969) observed that the cardiac arrest could be prevented by atropine.
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The negative inotropisms of anaesthetic agents such as ether or chloroform are counteracted in the intact subject by the positive inotropic action of increased circulating catecholamines. Suppression of the catecholamine response may cause circulatory failure (Brewster, Isaacs and Andersen, 1953), especially in the presence of deep anaesthesia complicated by metabolic acidosis.

In conclusion it may be said that the beta blocking drugs, whilst increasing the protective-ness of surgical anaesthesia, may enhance the hazards thereof if not applied with a full appreciation of their pharmacology in the medical and surgical environments. Modern anaesthetic tech-niques which combine the blockade of the vasoconstrictive reaction to surgical trauma with the pharmacological insulation of the heart from autonomic influences place the control of the circulation virtually in the hands of the anaesthesiologist.

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REFERENCES


ADDITIONAL READING